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The Development and Validation of a Reverse Phase-HPLC Analytical Method for Quantifying Dacomitrinib in Bulk Pharmaceutical Dosage Forms

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1. ABSTRACT:

A novel RP-HPLC technique that is easy to use, quick, accurate, precise, and repeatable for estimating dacomitinib in both commercial formulations and bulk form. Dacomitinib was successfully separated using an isocratic mode of separation on a Symmetry ODS C18 (4.6 x 250mm, 5□m) column using acetonitrile: methanol in an 80:20% v/v ratio at a flow rate of 1.0 mL/min. The detection was done at 272 nm. The linearity, sensitivity, accuracy, precision, specificity, and robustness of the method were all validated in accordance with ICH guidance. For Dacomitinib, the response was shown to be linear within the 10–50 mcg/mL drug concentration range. For Dacomitinib, the response was shown to be linear within the 10–50 mcg/mL drug concentration range. Dacomitinib's correlation coefficient was shown to be 0.999.Dacomitinib's LOD and LOQ were determined to be 1.1 µg/mL and 3.2 µg/mL, respectively. The suggested approach was found to have a decent percentage recovery for dacomitinib, demonstrating its excellent accuracy.[1]

1.1 Keywords: ICH Guidelines, Accuracy, Robustness, Validation, RP-HPLC, Dacomitinib.

2. INTRODUCTION :

Dacomitinib belongs to the class of quinazolines known as 7-methoxyquinazoline-4,6-diamine, in which a 3-chloro-4-fluorophenyl group replaces the amino group at position 4, and a (E)-4-(piperidin-1-yl) but-2- enoyl group1 replaces the amino group at position 6. It functions as an antineoplastic agent and an antagonist of the epidermal growth factor receptor. It belongs to the following groups: tertiary amino compounds, secondary amino compounds, secondary carboxamides, quinazolines, piperidines, enamides, mono chlorobenzenes, and mono fluorobenzenes. Known as (2E)-N-16-4-(piperidin-1-yl) but-2-enamide, dacomitinib is a highly selective Quinazalone oral medication that belongs to the second-generation class of tyrosine kinase inhibitors. These drugs are distinguished by their irreversible binding to the ATP domain of the kinase domains of the epidermal growth factor receptor family. Although more research is required, some evidence in the literature points to Dacomitinib's potential as a treatment in the epithelial ovarian cancer model. Patients with non-small cell lung cancer who have activating mutations in the epidermal growth factor receptor gene (EGFR) are treated with dacomitinib, a multi-kinase receptor inhibitor. Although dacomitinib is linked to a high risk of temporary elevations in serum aminotransferases during treatment, it has not been connected to any cases of acute liver injury that is clinically noticeable.[2]

All newly diagnosed cases, non-small cell lung cancer (NSCLC) makes up almost 85%. Over the past few decades, survival has not improved much; most patients receive their diagnosis after the disease is advanced enough that surgery is no longer an option, and as a result, their prognosis is poor.[3] When compared to upfront cytotoxic chemotherapy, the development of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) has revolutionized the treatment of advanced non-small- cell lung cancer (NSCLC) with an activating EGFR mutation, providing better survival and tolerability.[4]

3. DRUG PROFILE: (Table :1)

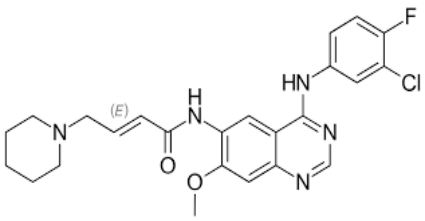
Particulars	Description
Drug name	Dacomitinib
Molecular structure	
Molecular formula	C24H25ClFN5O2
Molecular weight	469.95 g/mol
IUPAC Name	E)-N-[4-(3-chloro-4-fluoroanilino)-7-methoxyquinazolin-6-yl]-4-piperidin-1- ylbut-2-enamide
Solubility	DMSO: 2 mg/mL, clear
Category	Antineoplastic agents, which are used to treat cancer.
Mechanism of Action	Dacomitinib is an irreversible small-molecule inhibitor that works by targeting the tyrosine kinase activity of the Epidermal Growth Factor Receptor (EGFR) family, including EGFR/HER1, HER2, and HER4. It achieves irreversible inhibition by forming covalent bonds with cysteine residues in the catalytic domains of these receptors, effectively blocking the Ras signaling cascade and inhibiting tumor cell growth.[5]

Table 2: Different RP-HPLC methods for Dacomitinib :

Materials	Column	Mobile phase	Detection	Reference
Marketed Formulation	Symmentry ODS C18 Column	The ratio of phosphate buffer to acetonitrile is (48:52 V/V.)	UV, 248 nm	6
Dosage form	Kromsil C18 column	0.2% Triethylamine solution is combined with acetonitrile at a (70:30 V/V ratio)	UV, 260 nm	7
Dosage form	Symmetry ODS C18 column	The ratio of Phosphate Buffer (0.02M) and Acetonitrile was 48:52% v/v (pH-2.80)	UV, 248nm	8

Table-3: Chemicals Used :

Sr.No.	Chemical	Brand Names
1	DMF and Methanol for HPLC	LICHROSOLV (MERCK)
2	Dacomitinib (Pure)	Syncorp laboratories
3	Acetonitrile for HPLC	Merck

4. HPLC Method Development:

❖ **Standard Solution Preparation:**

- Accurately weigh and transfer 10 mg of Dacomitinib working standard into 10ml volumetric flasks.

- Add 7ml of Methanol and sonicate to dissolve and remove air.
- Pipette 0.72ml of Dacomitinib stock solutions into a 10ml flask and dilute with Methanol.
- Inject samples under different chromatographic conditions.
- Record chromatograms for validation parameters as per ICH guidelines.

❖ **Mobile Phase Optimization and Column Optimization :**

- Initial phase was methanol: DMF and Acetonitrile: Water.
- Final phase optimized to Methanol and DMF in 45:55 v/v.
- The technique was used with a variety of C18 columns, including ODS column, symmetry and X Bridge. It was determined that the Xterra C18 (4.6 x 150mm, 5□m) provided the best peak shape and resolution at a flow rate of 1 ml/min.

❖ **Mobile Phase prepared :**

by mixing 45% HPLC Methanol and 55% HPLC DMF, degassed, and filtered under vacuum filtration.

❖ **Preparation of the Diluent:**

The diluent was the mobile phase.

➢ **Procedure:**

After injecting the standard and sample solutions three times in duplicate, use the following formula to determine the assay[9] :

%ASSAY =

$$\frac{\text{Sample area}}{\text{Standard area}} \times \frac{\text{Weight of standard}}{\text{Dilution of standard}} \times \frac{\text{Dilution of sample}}{\text{Weight of sample}} \times \frac{\text{Purity}}{100} \times \frac{\text{Weight of tablet}}{\text{Label claim}} \times 100$$

➢ **Validation Parameters :**

System Suitability

- Accurately weigh and transfer 10 mg of Dacomitinib standard into 10ml volumetric flasks.
- Add 7mL of diluents and sonicate to dissolve completely.
- Pipette 0.72ml of Dacomitinib stock solution into another flask.

Procedure:

- **Measure area for all five injections in HPLC.**
- **%RSD for area of five replicate injections within specified limits.**

➢ **Specificity:**

Standard Solution Preparation:

- Accurately weigh and transfer 10 mg of Dacomitinib working standard into 10ml volumetric flasks.

- Add 7ml of diluents and sonicate to dissolve completely.
- Pipette 0.72ml of stock solutions into the same flask and dilute with diluents.

Sample Solution Preparation:

- Crush average tablet weight.
- Weight 10 mg equivalent of Dacomitinib sample.
- Add 7mL of Diluent and sonicate.
- Make volume up to mark with same solvent.
- Pipette 0.72ml of Dacomitinib above stock solution.
- Dilute with diluent.

➢ **Linearity:**

- Accurately weigh and transfer 10 mg of Dacomitinib into 10ml of clean, dry flasks.
- Add 7ml of diluents and sonicate to dissolve completely.
- Make volume up to the mark with the same solvent.
- **Prepare Levels I** (24ppm): Pipette 0.24ml of stock solution into a 10ml flask.
- **Prepare Level II** (48ppm): Pipette 0.48ml of stock solution into a 10ml flask.
- **Prepare Level III** (72ppm): Pipette 0.72ml of stock solution into a 10ml flask.
- **Prepare Level IV** (96ppm): Pipette 0.96ml of stock solution into a 10ml flask.
- **Prepare Level V** (120ppm): Pipette 1.2ml of stock solution into a 10ml flask.

▪ **Dacomitinib Product Solution Preparation** :

- Accurately weigh and transfer 10 mg of Dacomitinib working standard into 10ml of clean, dry flasks.
- Add 7ml of diluents and sonicate to dissolve completely.
- Pipette 0.72 ml of stock solutions into a 10ml flask and dilute.
- Inject the standard solution five times and measure area in HPLC.[10]
- %RSD for area of five replicate injections within specified limits.

Intermediate Precision Evaluation

- Perform precision on different days under same conditions.

Procedure:

- **Day 1:** Injection of standard solution six times.
- Area measurement in HPLC.

- %RSD for six replicate injections within specified limits.
- **Day 2:** Injection of standard solution six times.
- Area measurement in HPLC.
- %RSD for six replicate injections within specified limits.

➢ **Accuracy:**

For preparation of 50% Standard stock solution:

Dacomitinib Standard Dissolution

- Transfer 10 mg of Dacomitinib standard into 10ml volumetric flasks.
- Add 7mL of diluents and sonicate.
- Complete dissolution and volume up to mark.
- Pipette 0.36ml of stock solution into another flaskFor preparation of 100% Standard stock solution:

For preparation of 100% Standard stock solution:

Dacomitinib Stock Solution Distillation

- Accurately weigh and transfer 10 mg of Dacomitinib standard into 10ml volumetric flasks.
- Add 7mL of diluents and sonicate to dissolve completely.
- Make volume up to the mark with the same solvent.
- Pipette 0.72ml of Dacomitinib stock solution into a 10ml volumetric flask.

For preparation of 150% Standard stock solution:

Dacomitinib Stock Solution Distillation

- Accurately weigh and transfer 10 mg of Dacomitinib standard into 10ml volumetric flasks.
- Add 7mL of diluents and sonicate to dissolve completely.
- Make volume up to the mark with the same solvent.
- Pipette 1.08ml of Dacomitinib stock solution into a 10ml volumetric flask. [11]

Procedure:

Injection Procedure for Dacomitinib

- Injecting individual concentrations (50%, 100%, 150%) under optimized conditions.
- Recording chromatograms and measuring peak responses.
- Calculating Amount Found and Amount Added.

- Calculating individual and mean recovery values.

➢ **Robustness:**

Analysis Conditions for Variability of Test Results.

- Performed under various conditions.
- Checked for variation in results.[12]

❖ **For preparation of Standard solution:**

- Dacomitinib Standard Dissolution
- Accurately weigh and transfer 10 mg.
- Add 7mL of Diluents.
- Sonicate completely.
- Make volume equal to mark.
- Pipette Dacomitinib stock solution into 10ml flask.
- Dilute with diluents to mark.

❖ **Effect of Variation of flow conditions:**

➢ Sample Analysis

- Analyzed at 0.7ml/min and 0.9ml/min.
- Remaining conditions remain.
- 10µl sample injected.
- Chromatograms recorded.

❖ **Effect of Variation of Mobile Phase Organic Composition:**

➢ Sample Analysis

- Analyzed at 0.7ml/min and 0.9ml/min.
- Remaining conditions remain.
- 10µl sample injected.
- Chromatograms recorded.

❖ **Effect of Variation of Mobile Phase Organic Composition:**

➢ Sample Analysis:

- Variation of mobile phase: Methanol: Water, 40:60, 50:50.
- Same conditions as before.
- 10µl sample injected, chromatograms recorded.

5. RESULTS AND DISCUSSION:

➢ Optimization of Method:

Mobile phase ratio	**Methanol:DMF(45:55%v/v)**
Column	Xterra C18 (4.6×150mm) 5µmColumn
temperature	40ºC
Wavelength	260nm
Flow rate	0.8ml/min
Injection volume	10µl
Runtime	6minutes

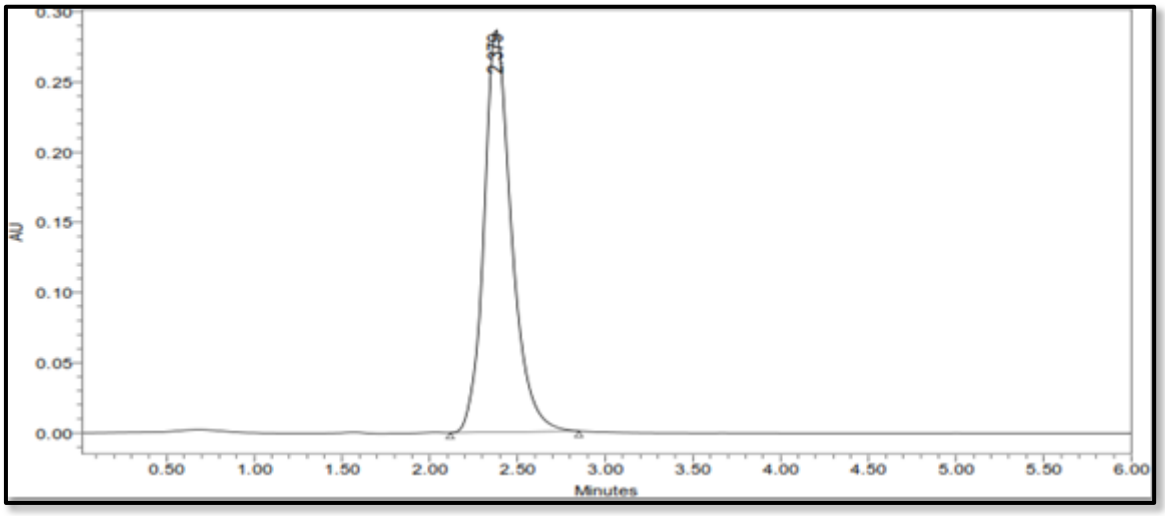


Fig-1: Optimized Chromatogram

❖ Validation of the Developed Method

➢ Method Validation:

- Linearity
- System suitability
- Precision
- Accuracy
- Robustness
- Specificity
- LOD

- LOQ
- ICH guideline compliance.

❖ **System Suitability Test**

➢ System Suitability Test Overview

- Initial mobile phase test followed by 5 injections of same concentration.
- Continuous injections conducted daily for method validation.
- Features calculated: % RSD, tailing factor, theoretical plate.

S.No.	Peak Name	RT	Area (µV*sec)	Height(µV)	USP Plate Count	USP Tailing
1	Dacomitinib	2.317	2274631	239458	5728	**1.2**
2	Dacomitinib	2.302	2284721	239582	5093	**1.2**
3	Dacomitinib	2.323	2238127	236493	5391	**1.2**
4	Dacomitinib	2.343	2259349	249482	6139	**1.2**
5	Dacomitinib	2.321	2204850	239452	5281	**1.2**
Mean			2252336			
Std.Dev.			31827.08			
%RSD			**1.41307**			

❖ **Specificity**

➢ ICH Specificity Definition

- Assesses unexpected presence of components.
- Includes impurities, degradation products, matrix components.
- Tested analytical method for accurate quantification of Dacomitinibind drug product.

%ASSAY =

$$\frac{\text{Sample area}}{\text{Standard area}} \times \frac{\text{Weight of standard}}{\text{Dilution of standard}} \times \frac{\text{Dilution of sample}}{\text{Weight of sample}} \times \frac{\text{Purity}}{100} \times \frac{\text{Weight of tablet}}{\text{Label claim}} \times 100$$

Dacomitinib's purity in pharmaceutical dosage form was determined to be 99.7%.

- **Calibration curve (linearity)**

➢ Drug Linearity Determination

- Prepared dilutions in concentration range of 24 to 120ng/mL.

- Constructed calibration curve using concentrations and peaks.
- Determined coefficient of correlation18 (R2).[13]

➢ **Chromatographic Data for Linearity Study:**

Table-4: Linearity Data of Dacomitinib

Concentration Level (%)	Concentration g/ml	Average PeakArea
33	24	**791554**
66	48	**1647073**
100	72	**2283804**
133	96	**3058339**
166	**120**	**3839630**

Linearity Plot:

The plot of Concentration(x) versus the Average Peak Area (y) data of Dacomitinib is a straight line.

Y=mx+ c

Slope (m) = 31709 Intercept(c)=34216 Correlation Coefficient (r)=0.998

❖ **Validation Criteria:**

The response linearity is verified when the Correlation Coefficient is 0.99 or higher.

❖ **Precision:**

The precision of an analytical procedure refers to the degree of agreement between measurements obtained from multiple samplings of a homogeneous sample under specific conditions [14].

❖ **Repeatability**

Five replicates of a 100% accuracy solution were obtained under experimental conditions, peak areas recorded, and the % RSD calculated.

Conclusion:

Five replicates of a 100% accuracy solution were obtained under experimental conditions, peak areas recorded, and the % RSD calculated.

Table-5: Results of Repeatability for Dacomitinib

Sr.No.	Peak Name	Retention time	Area (µV*sec)	Height (µV)	USPPlate Count	USP Tailing
1	Dacomitinib	2.356	2259464	245362	5938	**1.2**
2	Dacomitinib	2.356	2275915	248293	5827	**1.2**
3	Dacomitinib	2.357	2282117	240795	5032	**1.2**
4	Dacomitinib	2.358	2278675	230139	5978	**1.2**
5	Dacomitinib	2.359	2282448	249605	6183	**1.2**
Mean			2275724			
Std.Dev			9476.485			
%RSD			**0.416416**			

➢ **Intermediate Precision:**

Analyst 1:

Table-6:Results of Intermediate precision for Dacomitinib

S.No.	PeakName	RT	Area (µV*sec)	Height(µV)	USP Plate count	USP Tailing
1	Dacomitinib	2.380	2236184	202188	5472	**1.2**
2	Dacomitinib	2.383	2238020	201837	6193	**1.2**
3	Dacomitinib	2.385	2239352	201273	5980	**1.2**
4	Dacomitinib	2.385	2242466	203923	7163	**1.2**
5	Dacomitinib	2.389	2244692	202938	6182	**1.2**
6	Dacomitinib	2.389	2247654	201982	7684	**1.2**
Mean			2241395			
Std.Dev.			4333.851			
%RSD			**0.193355**			

Analyst 2 :

Table-7:Results of Intermediate Precision for Dacomitinib

Sr.No.	Peak Name	RT	Area (µV*s ec)	Height (µV)	USP Plate count	USP Tailing
1	Dacomitinib	2.380	2236184	217363	5928	**1.2**
2	Dacomitinib	2.383	2238020	218467	6183	**1.2**
3	Dacomitinib	2.385	2239352	218346	5927	**1.2**
4	Dacomitinib	2.385	2242466	221736	5163	**1.2**
5	Dacomitinib	2.389	2244692	228361	4827	**1.2**
6	Dacomitinib	2.346	2263431	217553	5019	**1.2**
Mean			2244024			
Std.Dev.			9988.458			
%RSD			**0.445114**			

❖ **Accuracy:**

Accuracy at different concentrations (50%,100%,and150%) was prepared and the % recovery was calculated.

Table-8: The Accuracy Results for Dacomitinib

%Concentration (at specification Level)	Area	Amount Added (ppm)	Amount Found (ppm)	%Recovery	Mean Recovery
50%	1172485	36	35.8	99.4	**99.5%**
100%	2314753	72	71.6	99.4	
150%	3480210	108	107.9	99.9	

❖ **Limit of Detection :**

The detection limit of an analytical procedure is the minimum amount of analyte in a sample that can be detected but not necessarily quantitated as an exact value.[14]

$$\mathbf{LOD = 3.3 \times \sigma / s}$$

Where,

σ = Standard deviation of the response

S = Slope of the calibration curve

Result=5.5µg/ml

❖ **Quantitation Limit :**

The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined.[15]

$$LOQ=10\times\sigma/S$$

Where,

σ = Standard deviation of the response

S = Slope of the calibration curve

Result = 16.7µg/ml

❖ **Robustness :**

➢ Dacomitinib chromatography method robustness tested for flowrate and mobile phase ratio variations.

- Method robust in less flow conditions and mobile phase changes ±5%.

- No significant changes in parameters like resolution, tailing factor, asymmetric factor, and plate count observed under chromatography conditions.

Table-9: Results for Robustness

Parameter used for Sample Analysis	Peak Area	Retention Time	Theoretical plates	Tailing factor
Actual Flowrate of 0.8mL/min	3119086	2.379	5837	**1.2**
Less Flowrate of 0.7mL/min	2640811	2.763	5361	**1.2**
More Flowrate of 0.9mL/min	2640354	2.234	5231	**1.2**
Less organic phase	2640758	2.765	4503	**1.5**
More organic phase	**2640125**	**2.236**	**4491**	**1.5**

6. Conclusion:

By examining several parameters, the analytical approach was created. First, the peak purity was excellent, and the highest absorbance was measured at 260 nm. 10µl was chosen as the injection volume since it produced a nice peak area. Because it was providing a good peak, the Xterra C18 column was chosen for the study. It was discovered that 40°C was appropriate for the type of medication solution. A suitable peak area and a sufficient retention the duration resulting in the flow rate being set at 0.8 ml/min. The mobile phase is methanol, and the good symmetrical peak allowed DMF to be fixed. For the suggested investigation, this mobile phase was employed.

Because the maximal extraction sonication duration was set at 10 minutes, at which point all of the drug particles were fully soluble and demonstrated good recovery, methanol: DMF was used. In order to minimize the overall run time and because the analysis showed a peak at 2.3, the run time of 6 minutes was chosen. It was discovered that the recovery percentage, which ranged from 98.0 to 102, was linear and accurate. The precision of the apparatus and the approach were both found to be accurate and well within range. The linearity of the analytical method was seen across the 24-120 ppm range of the target concentration of dacomitinib. Tests for toughness and robustness were both passed by the analytical. The relative standard deviation for both circumstances was quite excellent.

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